American Journal of Medical Genetics 64:196–197 (1996)

Prevalence of Fragile X Syndrome

G. Turner, T. Webb, S. Wake, and H. Robinson

Hunter Genetics Service, Newcastle (G.T.); Fragile X Program, Prince of Wales Children's Hospital, Randwick, New South Wales, Australia (H.R., S.W.); Clinical Genetics Unit, Birmingham Maternity Hospital, Birmingham, United Kingdom (T.W.)

The much-quoted prevalence figure of 1:1,000 males for fragile X syndrome is an overestimate in a mixed ethnic population. A reexamination of the individuals from whom those data were derived using molecular diagnostic techniques demonstrates a more realistic figure of 1:4,000 males.

KEY WORDS: prevalence, fragile X syndrome, mutations

INTRODUCTION

The definition of fragile X syndrome and estimates of its prevalence have had a turbulent history. The original definition rested on the finding of a fragile site at Xq27.3 in males who were mentally handicapped. A positive result was not always clear-cut, since only a proportion of cells examined demonstrated the fragile site; although most agreed on lower limits of 2–4%, sometimes even lower limits of 1–2% were accepted as positive [Soudek et al., 1984]. The number of cells counted varied considerably between laboratories, as did methods of cell culture. Furthermore, we now know that this cytogenetic definition included both FRAXE and FRAXF as well as FRAXD, a nonpathological, low-expressing, high-frequency fragile site at Xq27.2. Nearly all these factors led to overestimates of the prevalence of fragile X syndrome.

The clinical definition can now be redefined in the male as mental handicap associated with an absolute or relative deficiency of the gene product FMR-1 protein [Pieretti et al., 1991]. Testing for this protein is not yet generally available. The specific test used at present is the measurement of the size of a trinucleotide repeat [Snow et al., 1993]. Increase in this repeat number over a particular value initiates methylation of the promoter site, resulting in the switching off of the FMR-1 gene. This method of testing also defines individuals who lack FMR-1 protein as a consequence of deletion of the gene, but will not identify those whose FMR-1 protein is abnormal through point mutations.

It was assumed initially that there was a high mutation rate in fragile X syndrome, so that variation between different ethnic groups would be minimal. A founder effect has now been identified through the demonstration of linkage disequilibrium, so that varying prevalence figures are to be anticipated in different ethnic populations [Richards et al., 1991].

There have been many studies of the prevalence of fragile X syndrome by screening populations of individuals with mental handicap in institutions and special schools; highly variable percentages have been reported. There are two studies within ethnically distinct communities using data from the cytogenetic testing of children with intellectual handicap in an area where the background demography was known: in Sweden, Gustavson et al. [1986] found a prevalence of 6.7:10,000, and in Finland, Kähkönen et al. [1987] found 8.3:10,000.

Webb et al. [1986] and Turner et al. [1986] published prevalence papers, from Coventry, England, and from Sydney, Australia, respectively. Webb et al. [1986] found a prevalence of 1:1,000, and Turner et al. [1986], 1:2,610. The survey by Webb et al. [1986] was of children identified as handicapped in the school population and in residential accommodation with a Coventry address. The age range selected was 11–16 years. Those offered testing were those where the diagnosis was unknown. A correction was made for those refusing testing. A positive result was 3% of cells being fragile X-positive; 50 cells were first counted, and if one cell was positive, a further 50 were counted. The prevalence figure in Turner et al. [1986] was derived from data generated through a screening program offered to all those with mental handicap in a population of 1.1 million. Those of school age were selected to calculate prevalence, with mild handicapped aged 8–12 years, and moderate and severely handicapped aged 5–16 years. These groups were in special classes or schools. The background number in these age ranges in the school populations from which they were selected was known.

Those tested were those without a syndrome diagnosis who were not microcephalic and did not have cerebral palsy; 77% of parents consented to testing; 100 cells were counted, and 2% was taken as a positive finding.

Received for publication September 26, 1995; revision received December 11, 1995.

Address reprint requests to Prof. G.M. Turner, Hunter Genetics, P.O. Box 84, Waratah, New South Wales 2298, Australia.

TABLE I. Reassessment of Prevalence of Fragile X Syndrome After Molecular Testing

	Webb et al. [1986], Coventry, England (total, 28,611 boys)			Turner et al. [1986], Sydney, Australia (total, 58,094 boys)		
Intellectual handicap	Moderate/severe		Mild	Moderate/severe		Mild
N karyotyped	60		159	149		323[a]
N FraX+	6		10	9		5
Prevalence		1 in 952, or			1 in 2,610, or	
N DNA tested	6	10.5/10,000	10	9	3.8/10,000	5
N DNA+	4		2	8		2
Prevalence		1 in 4,090, or 2.4/10,000			1 in 4,350, or 2.3/10,000[b]	

[a]Only those 8–12 years old were screened.
[b]Not corrected for those who refused permission. If this is done, prevalence becomes 3.0/10,000.

METHODS

In these two series the males identified as being fragile X positive have been re-examined by Southern Blot testing and the prevalence was recalculated.

RESULTS

Prevalence in Mentally Handicapped Males With Fragile X Syndrome

Table I shows the data from the two surveys updated following molecular testing of those boys who were originally identified as fragile X-positive by cytogenetic examination. The revised estimates of prevalence in both series are in remarkable agreement. This is despite differences in the two populations studied; that of Webb et al. [1986] was mainly Caucasian with an admixture of Pakistani families, whereas that of Turner et al. [1986] was predominantly Caucasian with an admixture of Mediterranean families. The correction noted in the footnote to Table I, allowing for those in the series of Turner et al. [1986] who gave no permission for testing, was deemed unnecessary, since subsequent and continued state-wide proband identification and studies of excluded families showed that no boys were later identified as having fragile X syndrome in this subgroup.

Prevalence of the Full Mutation in Females

Prevalence of the full mutation in females is the same as the prevalence in males, because the full mutation only occurs in the offspring of females, and the reproductive rate of males with the full mutation is virtually zero. Estimates of the prevalence of mental retardation associated with the full mutation vary depending on the definition of mental retardation, intellectual handicap, and learning problems, and on the type of psychological testing used. However, it is generally accepted that at least 50% of those females with a full mutation will have some degree of intellectual impairment, so that the clinical prevalence of fragile X syndrome in the female is approximately 50% of that found in the male.

DISCUSSION

The much-quoted statement that fragile X syndrome has a prevalence rate of 1/1,000 and is the second most common cause of mental handicap was based on cytogenetic data which have proven to be less specific than expected. A more realistic figure based on molecular analysis is 1/4,000 or 2.4/10,000. These results are consistent with the overall prevalence rates found in the general population of NSW [Robinson et al., 1996]. Recent studies surveying populations of mentally handicapped school children using molecular diagnostic techniques have failed to identify the expected number of children with fragile X syndrome using the older prevalence figures [Hagermann et al., 1994; Jacobs et al., 1993; Barnicoat, 1994].

A second factor which may be a cause of decline in prevalence is the effect of counselling and informed choice in the extended families of individuals identified as having fragile X syndrome over the last 10 years.

REFERENCES

Barnicoat A (1994): The fragile X syndrome. MD Thesis, University of London.

Gustavson KH, Blomquist HK, Holmgren G (1986): Prevalence of the fragile X syndrome in mentally retarded children in a Swedish county. Am J Med Genet 23:581–587.

Hagermann RJ, Wilson P, Staley LW, Kirsten AL, Fan T, Uhlhorn C, Jewell-Smart S, Hull C, Drisko J, Flom K, Taylor AK (1994): Evaluation of school children at high risk for fragile X syndrome utilizing buccal cell FMR-1 testing. Am J Med Genet 51:474–481.

Jacobs PA, Ballman H, MacPherson J, Youing S, Rooney V, Watson A, Donnis NR (1993): Population studies of the fragile X: A molecular approach. J Med Genet 30:454–459.

Kähkönen M (1987): Prevalence of the fragile X syndrome in four birth cohorts of children of school age. Hum Genet 77:85–87.

Pieretti M, Zhang FP, Fu YH, Warren ST, Oostra BA, Caskey CT, Nelson DL (1991): Absence of expression of the FMR-1 gene in fragile X syndrome. Cell 66:817–822.

Richards RI, Holman K, Friend K, Kremer E, Hillen D, Staples A, Brown WT, Goonewardena P, Tarleton J, Schwartz C, Sutherland GR (1991): Fragile X syndrome: Genetic localisation by linkage mapping of two miscosatellite repeats FRAXAC1 and FRAXAC2 which immediately flank the fragile site. J Med Genet 28:818–823.

Robinson H, Wake S, Wright F, Laing S, Turner G (1996): Informed choice in the fragile X syndrome and its effects on prevalence. Am J Med Genet 64:198–202.

Soudek D, Partington MW, Lawson J (1984): Fragile X syndrome I: Familial variation in the proportion of lymphocytes with fragile sites in moles. Am J Med Genet 17:241–252.

Snow K, Doud LK, Hagermann R, Pergolizzi RG, Erster SH, Thibodeau SN (1993): Analysis of a CGG sequence at the FMR-1 locus in fragile X families and in the general population. Am J Hum Genet 53:1217–1228.

Turner G, Robinson H, Laing S, Purvis-Smith S (1986): Preventive screening for the fragile X syndrome. N Engl J Med 315:607–609.

Webb T, Bundey S, Thake J, Todd A (1986): The frequency of the fragile X chromosome among schoolchildren in Coventry. J Med Genet 23:396–399.